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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OLSON, ERIC	
ART UNIT	**PAPER NUMBER**
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,739	TIGYI ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *3,4,12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-11 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application claims priority to provisional application 60/462274, filed April 11, 2003.

Election/Restrictions

Applicant's provisional election with traverse of group II, drawn to a method of treating neointima formation, submitted February 27, 2007, is acknowledged. Applicant's arguments of record with respect to the aforementioned traversal are acknowledged and found to be persuasive to remove the requirement for restriction between groups II and IV. Therefore both groups will be examined on the merits herein.

Claims 3, 4, 12, and 13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made with traverse in the reply filed on February 27, 2007.

Claims 1, 2, 5-11, and 14-18 are pending in this application and examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 8, 14, 15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims recite the phrase, "analog of lysohosphatidic acid." Neither the claims, the specification, or the prior art provides a clear and distinct definition of what is reasonably considered to be an analog of lysophosphatidic acid. In fact, there exist in the art a number of different possible interpretations of this phrase, encompassing various chemical or structural transformations that may or may not be considered to be analogs of LPA by one skilled in the art. Therefore the claims are indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 6, 8-11, 17, 15, 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a therapeutic method comprising administering certain specific PPAR-γ antagonists such as those recited in claim 7, does not reasonably provide enablement for a method comprising administering any compound that inhibits signaling trough PPARγ. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating a disorder by administering a pharmaceutical compound.

The state of the prior art: Interaction of lysophosphatidic acid with its receptors is known in the art to affect cell proliferations including that taking place in atherosclerosis and neointima formation. .Certain specific compounds are known in the art to disrupt thins interaction and interfere with cell proliferation. However, the prior art does not include a complete, exhaustive listing of every compound that is a PPARγ antagonist. Based on the number of uncharacterized compounds in existence, the total number of PPARγ antagonists is likely to be very large.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The design of ligands to receptors is unpredictable. A compound similar to an existing antagonist can easily turn out to not bind the receptor, or to bind as an agonist. Predicting the activity of a novel compound not similar to any existing ligand is even more difficult, if not impossible.

Furthermore, the art of organic synthesis of novel compounds is complex. For a novel, complex compound to be synthesized, one skilled in the art must develop and optimize a synthetic method by trial and error, involving unpredictable experimentation.

The Breadth of the claims: The claimed invention is very broad, encompassing methods comprising administering any chemical substance whatsoever. These substances include organic small molecules, polynucleotides, polypeptides, oligosaccharides, inorganic complexes, and any other compound that could reasonably be administered to a living subject.

The amount of direction or guidance presented: The instant specification provides a rationale for concluding that PPARγ antagonists will disrupt the formation of neointima, and furthermore discloses a number of specific PPARγ antagonists. The specification does not provide an exhaustive list of all possible PPARγ antagonists or of any method of predicting the full range of said antagonists.

The presence or absence of working examples: No working examples are provided of actual methods for treating disease.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the discovery of a broad class of compounds. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of PPARγ antagonists beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as a PPARγ

antagonist. According to the 2006 Chemical Abstracts catalog, (Reference included with PTO-892) The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have PPARγ antagonist activity. For most compounds, it is unknown whether they are or are not useful as PPARγ antagonists. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for PPARγ antagonist activity, as well as *in vivo* testing of compounds having this activity involving either human or animal subjects to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential PPARγ antagonists, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of

experimental animals, to establish the activity or lack thereof of every possible adenosine A_{2A} antagonist, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of PPARγ antagonists claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the unpredictability of the art, Applicants fail to provide information sufficient to practice the claimed invention for all possible compounds that inhibit signaling through PPARγ.

Claims 1, 2, 5-11, and 14-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating neointima formation and atherosclerosis, does not reasonably provide enablement for a method of inhibiting or preventing said conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to a therapeutic method for prevention or inhibition of a disorder.

The state of the prior art: Certain PPARγ antagonists are known in the art to be useful for treating atherosclerosis by disrupting the formation of neointima. They are not known to completely prevent atherosclerosis, which is in fact a complex disease having various causes and symptoms.

In general, preventing chronic, progressive disorders, according to the definition of prevention given below under the heading "breadth of the claims" is not possible as, in the absence of a cure which reverses the underlying cause, the disorder will ultimately progress to a point where tolerated doses of the therapeutic agent are no longer effective to retain the level of functioning experienced before the onset of disease. More generally, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of

treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

Additionally, because various physiological systems are interdependent and affect one another, any hypothetical preventative treatment would have to be broad-based and treat all of the various causes of a disorder. For example, because osteoporosis is, in the majority of cases, caused at least in part by a reduction in

estrogen levels, a true preventative treatment for osteoporosis must be capable of preventing or reversing menopause in a subject.

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an indefinite period of time. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at preventing a disorder.

The amount of direction or guidance presented: No guidance is given in the specification suggesting any reason to believe that administration of a PPARγ antagonist can fully, completely, and permanently prevent atherosclerosis and/or neointima formation.

The presence or absence of working examples: No working examples are given of actual preventative methods.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the inhibition or prevention of disease.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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